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Reactions of Acid Chlorides/Ketenes with 2-Substituted 4,5-Dihydro-4,4-dimethyl-1,3-thiazoles; Formation of Penam Derivatives

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Addition reactions of acid chlorides with various 2-substituted 4,5-dihydro-4,4-dimethyl-5-methylthio-1,3-thiazoles under basic conditions were studied. Two kinds of products were obtained from these addition reactions, β-lactams and non-β-lactam adducts. When the reaction was carried out with 4,5-dihydro-1,3-thiazoles with a phenyl substituent at C(2), the reaction proceeded *via* formal [2+2] cycloaddition and led to the correspoding β-lactam. On the other hand, acid chlorides and 4,5-dihydro-1,3-thiazoles bearing an α-H-atom at the C(2)-substituent underwent *C(α)*- and/or *N*-addition reactions and gave rise to non-β-lactam adducts, *i.e.* C(α)- and/or N-acylated 1,3-thiazolidines. The attempted transformations of sulfonyl esters of *exo*-6-hydroxypenams to *endo*-6-azidopenams failed, although they were successful with mono-β-lactams under the same conditions.

1. Introduction. – A convenient synthesis of 4,4-disubstituted 1,3-thiazole-5(4*H*)-thiones **1**, the less well-known di-sulfur analogs of 1,3-oxazol-5(4*H*)-ones (azlactones), was developed in the eighties [2]. The method also allowed the preparation of enantiomerically pure examples [3]. In a large series of experiments, it has been shown that the C=S group of **1** is the most reactive part of the molecule [4]. Therefore, derivatives **1** have been used as models for 1,3-dipolaar cycloadditions [5], hetero-*Diels-Alder* reactions [6], and [2+2] cycloadditions [7] with C=S compounds, as well as for the study of BF_3-catalyzed reactions with oxiranes [8] and thiophilic *versus* carbophilic additions of organometal compounds [9].

After transformation of the C=S group of **1a** (R^1 = Ph, R^2 = R^3 = Me) into the methylsulfanyl derivative **2a** (R^2 = R^3 = Me), treatment of the latter with one mole-equiv. of dichloroacetyl chloride (**3a**) followed by Et_3N led to a 2:1 mixture of the β-lactam derivative **4a** (a 'penam') and the 2-methylen-1,3-oxazin-6-one **5**[3]) in a total yield of 44% [10] (*Scheme 1*). Under analogous reaction condtitions, *cis*-**2b** (R^2 = Me, R^3 = i-Pr) gave a single product **4b** with all-*cis*-configuration (all substituents MeS, i-Pr, and Ph in *exo* positions) in 94% yield. The reaction of **2a** with azidoacetyl chloride yielded the penam of type **4** with *exo*-orientation of the azido group at C(6) [10].

Scheme 1

[3]) The structure of **5** was established by X-ray crystallography (H. Heimgartner, J. H. Bieri, R. Prewo, A. Linden, C. Jenny, Private Communication CCDC, Cambridge, England, 1993. CSD refcode: HACPUW).

β-Lactam antibiotics belong to the most efficient agents in fighting bacterial infections[4]). Mostly, the β-lactam antibiotics are the products of fermentation and semi-synthesis, and despite many efforts, only a couple of monocyclic β-lactams are produced by total synthesis. Nevertheless, there is a continuing interest in new synthetic methods towards this highly desired class of compounds (see, *e.g.*, [12]). Among the various methods for the preparation of β-lactams, the acid chloride/imine (ketene/imine) addition is one of the most widely used. Since its discovery by *Staudinger* in 1907 [13], the scope and limitations of this method have been studied extensively, and much progress has been made on the synthesis of monocyclic β-lactams [14]. However, for the synthesis of bicyclic β-lactams, *e.g.*, penams, this method suffers in two ways: the poor yield of the reaction and the low or inappropriate stereoselectivity. Although the problem of the wrong configuration at C(6) has been solved by the transformation of 6-epipenicillin to penicillin [15], the epimerization is a multistep process and gives the product only in low yield. Therefore, a number of studies concerning the formation of the penam skeleton *via* the reaction of 4,5-dihydro-1,3-thiazoles with various acetylchlorides/base, *i.e.*, the imine/ketene addition, have been published [16]. Furthermore, the continuing interest in penam derivatives is shown by the elaboration of new methods for their preparation (*e.g.* [17]), the synthesis of analogs such as selenapenams [18], and the modifcation of known compounds, *e.g.*, 6-aminopenicillic acid (6-APA) [19].

The aim of the present study was the extension of the reaction **2** $\rightarrow$ **4** on 4,5-dihydro-1,3-thiazoles of type **2** with a $PhCH_2$ or a Me group at C(2), as well as on acetyl chlorides bearing an acetoxy or phthalimido group. Furthermore, a method for

[4]) For recent reviews, see [11].

transformation of 6-*exo*-substituted penams into the corresponding 6-*endo*-azido derivatives should be elaborated.

2. Results and Discussion. – 2.1. *Reactions of 4,5-Dihydro-1,3-thiazoles* **2** *with Acetyl Chlorides and* Et_3N. The substituted 4,5-dihydro-4,4-dimethyl-5-methylthio-1,3-thiazoles **2** were synthesized from by treatment of the corresponding 4,4-dimethyl-1,3-thiazole-5(4*H*)-thione **1** with MeLi in THF at –78° [9a]. When **2a** was treated with acetoxyacetyl chloride (**3b**) in CH_2Cl_2 at room temperature in the presence of Et_3N, two products *endo*-**6a** and *exo*-**6a** were formed in a ratio of *ca.* 2:1, isolated in 62% yield after chromatographic workup. The two stereoisomers were separated by prep. TLC. On the basis of the spectroscopic data, the structures of isomeric penams **6** were assigned (*Scheme 2*). As it has been shown that in [2+2] cycloadducts of 4,5-dihydro-1,3-thiazoles with ketenes the ring S-atom is unmistakably oriented *trans* to the group with a heteroatom at C(6) [20], *endo*-**6a** and *exo*-**6a** were assigned both as 5,6-*trans* products. Then, the remaining possibility for the presence of isomers must be the result of different configurations of the MeS substituent at C(2), as the reaction started from racemic **2a**. Hence, *endo*-**6a** and *exo*-**6a** were assigned as the diastereoisomers with 2-*endo*- and 2-*exo*-5,6-*trans*-bicyclic penams, respectively. Finally, the structure of *endo*-**6a** was confirmed by X-ray crystallography (*Fig. 1*). Similarly, the reaction of **2a** and phthalimidoacetyl chloride **3c** also gave a mixture of two diastereoisomers *endo*-**6b** and *exo*-**6b** (3:1) in a low yield of 15% (*Scheme 2*).

Scheme 2

Fig. 1. *ORTEP Plot* [21] *of the molecular structure of* endo-**6a** (with 30% probability ellipsoids; arbitrary numbering of atoms)

Since the space group of *endo*-**6a** is centrosymmetric, the compound in the crystal is racemic. Whereas the acetoxy group at the *β*-lactam ring is *exo* oriented, *i.e.*, *cis* to the Ph group, the methylsulfanyl group at the thiazolidine ring occupies the *endo* position.

On the other hand, acid chlorides **3a** – **3c** reacted with the 2-benzyl substituted 4,5-dihydro-1,3-thiazole **2b** under the same conditions (CH_2Cl_2, r.t.) to give different products. The reaction of **2b** with excess dichloroacetyl chloride (**3a**) gave two products in almost equal amounts. According to the NMR spectra, the second product consists of a 1:1 mixture of diastereoisomers. The MS and the NMR spectra showed that they were derived from 1:1 and 1:2 adducts of **2b** and **3a** by elimination of one and two, respectively, equivalents of HCl. The IR spectra excluded the presence of *β*-lactam structures, as both products both lack the absorption at *ca.* 1750 cm^{-1}, *i.e.*, the characteristic *β*-lactam C=O stretching band. In both compounds, an amide/lactam group was indicated by IR absorptions at 1700 and 1720/1710 cm^{-1}, respectively, and ^{13}C-NMR signals at 163.9 and 159.5 ppm, respectively. On the basis of the specroscopic data, structures **7a** and **8** were proposed for these products (*Scheme 3*). Treatment of **7a** with excess **3a** and Et_3N in boiling hexane led to **8** in 31% yield.

Scheme 3

The same starting materials **2a** and **3a** reacted in refluxing hexane in the presence of Et_3N, and the same product **7a** was formed together with a new compound

9. Again, lack of absorptions for a corresponding C=O group showed that no *β*-lactam was formed; the C=O signals appeared at 1600 cm^{-1} and 179.5 ppm. Furthermore, a NH signal was detected at 10.92 ppm in the ^{1}H-NMR spectrum. The structure of **9** was proved undoubtedly by X-ray crystallography (*Fig. 2*).

Fig. 2. *ORTEP Plots* [21] *of the molecular structures of a)* **9** *and b)* **7b** (with 50% probability ellipsoids; arbitrary numbering of atoms)

Similar reactions of **2b** with acetoxyacetyl chloride (**3b**) and phthalimidoacetyl chloride (**3c**), respectively, in refluxing hexane gave a single 1:1 adduct **7b** or **7c** in each case (*Scheme 4*). Furthermore, 2-methyl-4,5-dihydro-1,3-thiazole **2c** reacted with **3a** under similar conditions to give the '1:2 adduct' **10** in low yield. The structures of all these products were assigned on the basis of their spectroscopic and analytical data and, in the case of **7b**, the structure was established by X-ray crystallography (*Fig. 2*).

The space groups of **9** and **7b** are centrosymmetric, therefore, the compounds in the crystals are racemic. The thiazolidine NH group of **9** forms an intramolecular H-bond with the O-atom of the side chain C=O group; graph set motif [22] S(6). In the case of **7b**, the exocyclic C=C bond is (*Z*)-configured.

Scheme 4

It should be mentioned that all attempts to synthesize spiropenams by the acid chloride/imine cycloaddition failed. Under various conditions, C(4)-spirocyclic 4,5-dihydro-1,3-thiazoles [9c] reacted neither with **3a** nor with **3b** in the presence of Et_3N. In most of the cases, the starting materials were recovered in high yields. Similarly,

the bulky 2-(*tert*-butyl)-4,5-dihydro-4,4-dimethyl-5-(methylthio)-1,3-thiazole [9c] also failed to react with **2a**,**b** under similar conditions.

2.2. *Synthesis of Monocyclic α-*Hydroxy-*β-lactams and Attempted Transformations to α-Azido-β-lactams*. With the aim of elaborating reaction conditions for the transformation of penams of type **6** into the corresponding 6-*endo*-azido derivatives, monocyclic *β*-lactams were prepared as model compounds. Thus, *N*-benzalaniline (**11**) in CH_2Cl_2 in the presence of Et_3N was reacted with acid chlorides **3b** and **3c**, respectively, at room temperature to give the corresponding monocyclic *β*-lactams **12a** and **12b** in good to excellent yield (*Scheme 5*)[5]). In the case of **3c**, only the *trans* isomer **12b** was obtained, whereas in the case of **3b**, a 1:1 mixture of *cis*- and *trans*-**12a** was isolated. The *cis*/*trans*-configurations were assigned on he basis of the coupling constants of H–C(3),H–C(4) in the ^{1}H-NMR spectra [24] (see also [23]).

Scheme 5

In several publications, the transformation of *cis*- and *trans*-substituted 3-hydroxyazetidinones to the corresponding 3-azido derivatives with inverted configuration has been described (*e.g.* [25]). For this reason, our intention was to use the mixture of *cis*/*trans*-**12a** as a model for this purpose. Firstly, **12a** was hydrolyzed by treatment with $NaHCO_3$ in MeOH/H_2O at 0° to give *cis*/*trans*-3-hydroxy-*β*-lactams **13** [23a][23c][25b][26] (*Scheme 6*). The diastereoisomers *trans*-**13** and *cis*-**13** were

[5]) For analogous recent studies, see [12b][23]. Selective syntheses of *cis*-**12a** under similar conditions [23a] or at –78° [23b] were reported, those of *cis*- and *trans*-**12b** were described in [23d][23e].

separated successfully by flash-chromatography. Subsequent sulfonylation of the two isomers with 4-chlorophenylsulfonyl chloride (*cf.* [23a][25]) gave the sulfonates *trans*-**14** and *cis*-**14**, respectively, in excellent yields. Treatment of the latter with NaN_3 in DMF at 50–60° afforded *via* stereoselective S_N2 reaction the 3-azido-*β*-lactams *cis*-**15** and *trans*-**15**, respectively, with complete conversion of the configurations (*Scheme 6*).

Scheme 6

The successful exchange of the OH group in monocyclic *β*-lactams for the azido group (see above and [25]) encouraged us to try this method in the case of the bicyclic *β*-lactams **6a**. In analogy to the monocyclic *β*-lactams **12**, the diastereoisomeric mixture **4**, as well as the separated 2-*endo*- and 2-*exo*-diastereomers *endo*-**6a** and *exo*-**6a**, were hydrolyzed under mild conditions to give the corresponding 6-hydroxypenams **16** (*Scheme 7*). The diastereoisomers *endo*- and *exo*-**16** formed from the mixture of *endo*- and *exo*-**6a** could be separated easily by prep. TLC[6]).

The structure of *exo*-**16** was established by X-ray crystallography (*Fig. 3*). Since the space group is centrosymmetric, the compound in the crystal is racemic. The substituents MeS, Ph, and OH are all *exo*-oriented. The OH group forms an intermolecular H-bond with the carbonyl O-atom of a neighboring molecule and thereby links the molecules into extended chains which run parallel to the [100] direction and can be described by a graph set motif [22].

Scheme 7

[6]) The hydrolyses of the pure diastereoisomers *endo*-**6a** and *exo*-**6a** led to pure *endo*-**16** and *exo*-**16**, respectively, in a stereospecific manner.

Fig. 3. *ORTEP Plot* [21] *of the molecular structure of exo*-**16** (with 50% probability ellipsoids; arbitrary numbering of atoms)

Sulfonylation of **16** in CH_2Cl_2/Et_3N at 0° with 4-chlorophenyl- and 2,4-dinitrophenylsulfonyl chlorides gave the corresponding sulfonates **17a** and **17b**, respectively, in high yields. Under the same conditions, the reaction of **16** with (trifluoromethyl)sulfonyl chloride was carried out, but the corresponding sulfonyloxypenam **17c** was obtained in only 27% yield as a crude and unstable product. Surprisingly, 4,5-dihydro-4,4-dimethyl-5-methylsulfonyl-2-phenyl-1,3-thiazole (**2a**) was formed *via* a decomposition reaction.

Substitution of the sulfonate **17a** with NaN_3 under same conditions as in the case of monocyclic β-lactams **14** failed; no substitution product, *i.e.*, a 6-azidopenam, was formed, and mainly starting material was recovered. Even reactions with the more active substrates **17b** and **17c** did not result in any desired azido product. Instead, some decomposition product **2a** was formed. As the unstable triflated bicyclic penam **17c** decomposed already under the conditions of its preparation, triflation and substitution with NaN_3 were conducted in a one pot reaction under mild conditions (0°). However, this also failed to afford the desired azido compound, and again some cleavage product **2a** was isolated. All further attempts to use the more nucleophilic and better soluble azido reagents LiN_3 and Bu_4NN_3 also failed to give an azido penam.

3. Conclusions. – The acid chloride/imine cycloaddition has been studied extensively, and three mechanistic pathways have been proposed [27]: 1) direct acylation of the imine with the acid chloride leads to the intermediate *N*-acyliminium

chloride **A** or the chloroalkyl amide **B**, which reacts with base to give the β-lactam; 2) the initial formation of a ketene and subsequent [2+2] cycloaddition with an imine, perhaps *via* the zwitterionic intermediate **C**, yields the β-lactam; 3) deprotonation of the initially formed **A** leads to **C** which reacts to give the β-lactam (*Scheme 8*). However, it is not possible to predict the stereochemical course of all of the reported reactions with a single mechanisms, and it is likely that more than one mechanism is involved[7]).

Scheme 8

In the acid chloride/imine cycloaddition, especially with cyclic imines, the heteroatom at the imine C-atom plays an important role in the determination of the relative configuration of the resulting β-lactam. It has been reported that a 4,5-dihydro-1,3-thiazole gives exclusively the 5,6-*trans*-configured penam in the reaction with *N*-protected glycyl chloride [20]. This observation was confirmed in the present study, in which only the 5,6-*trans* β-lactams **6a** and **6b** were formed in the reaction of 4,5-dihydro-1,3-thiazole **2a** with acetoxyacetyl chloride (**3b**) and phthalimidoacetyl chloride (**3c**), respectively (*Scheme 2*).

The substituent at C(α) of the acid chloride also has an influence on the configuration of the formed β-lactam. It was found that a relatively bulky acid chloride leads to the 3,4-*trans*-configured β-lactam, while a less sterically hindered acid chloride had a minor influence on the configuration of the product. For instance, **3c**

[7]) For some recent relevant articles and recent reviews, see [28][29].

and benzalaniline (**11**) gave exclusively the *β*-lactam *trans*-**12b**, while **3b**, under analogous conditions, afforded a 1:1 mixture of *cis*- and *trans*-**12a** (*Scheme 5*).

The efficiency of the cycloaddition reaction with cyclic imines depends to a great extent on the substituent at the imine C-atom. *E.g.*, the reaction of a 2-unsubstituted 4,5-dihydro-1,3-thiazole with azidoacetyl chloride gave the correspoding penam in a very poor yield [30], while the 2-phenyl-substituted **2a** afforded the bicyclic *β*-lactams **6a** in much higher yield (see also [10]). However, a sterically bulky substituent at C(2) may obstruct the reaction, as the 2-*tert*-butyl analog of **2a** failed to react with **3a** and with **3b**, respectively. For similar reasons, 4,4-spiro-4,5-dihydro-1,3-thiazoles of type **2a** failed to give any *β*-lactam under analogous reaction conditions.

When the substituent at C(2) of the 4,5-dihydro-1,3-thiazole **2** bears a C(*α*) H-atom, the reaction with acid chlorides/Et_3N proceeded *via* another pathway leading to *N*- and/or *C*-acylated products. The formation of *N*-acylated products in reactions with acid chlorides/Et_3N has previously been reported [31]. They might be formed by the nucleophilic attack of the imine *N*-atom onto the ketene or acid chloride (**2b**→**D**, *Scheme 9*), followed by a proton-shift in the zwitterion **D** to give **7a**. Apparently, this process is favored over ring closure to form a *β*-lactam.

To the best of our knowledge, the *C*-acylation of a 4,5-dihydro-1,3-thiazole by an acid chloride or a ketene has not been reported yet. A reasonable mechanism for the reaction **2b**→**9** is depicted in *Scheme 9*: the enamine moiety in the tautomeric structure **2b'** may attack the ketene or acyl chloride to give **E**, followed by a prototropic isomerization. Control experiments showed that the *C*-acylation is even more favored in the absence of Et_3N (16% of **7a** and 64% of **9**). Therefore, an initial deprotonation of **2b** by the base, to give a benzyl anion, which then could attack the ketene to give **E**, is not necessary.

Scheme 9

The formation of 2:1-adducts in reactions of ketenes and 4,5-dihydro-1,3-thiazoles, *i.e.*, 2-methylene-1,3-oxazin-6-ones or piperidine-2,4-diones, has already been reported [10][32]. However, the structure of compound **8** is different from those of the above reported bicycles, in which the substituents at C(2) were not involved in the formation of the fused ring system. A control experiment showed that **8** was also formed *via* a secondary acylation of the *N*-acylation product **7a**: in refluxing hexane, in the presence of **3a** and Et_3N, **8** was afforded. A likely reaction mechanism is shown in *Scheme 10*. Deprotonation of **7a** and subsequent addition to a second ketene molecule could form intermediate **F**, which may undergo a cyclization *via* nucleophilic attack of the enamine moiety onto the C=O group. An alternative reaction sequence *via C*-acylation of **7a** to give **G**, deprotonation of the *N*-acyl moiety, and cyclization is also conceivable.

Scheme 10

The exchange of the OH group by the azido function was successful in monocyclic β-lactams **13** (*Scheme 6*), but it failed in our bicyclic β-lactams **16** (*Scheme 7*). The reason could be the stereochemical hindrance around the 6-sulfonate substituent in **17**; both the fused thiazolidine ring and the 5-phenyl substituent contribute to this hindrance. The first contribution was confirmed by the successful substitution in **13**, and the latter was supported by a report, in which a 5-unsubstituted

6-*exo*-hydroxypenam was converted to the 6-*endo*-azidopenam under similar conditions as ours [33].

The acid chloride/imine cycloaddition provides a versatile and convenient way to produce monocyclic *β*-lactams in which high yields. By choosing appropriate substituents on both the acid chloride and the imine, a stereoselective formation of products could be achieved. However, for bicyclic *β*-lactams, the yields are generally poor, especially for the most desired 5-unsubstituted penams. To solve the problem, *Nagao et al*. [16e] introduced the methylseleno-substituent into the 2-position of 4,5-dihydro-1,3-thiazoles. With this promotive group, the yield of the cycloadditions dramatically improved. The methylseleno-group could be removed afterwards by selective reduction using Bu_3SnH. Concerning the stereochemistry of the products, the method afforded exclusively the undesired stereoisomers, namely the *trans β*-lactams with the substituent at C(6) *exo* oriented. Thus, to get biologically interesting products, an epimerization at C(6) is needed. As the *exo* → *endo* transformation was reported to be successful in bicyclic *β*-lactams [33], the combination of *Nagao*'s cycloaddition, deselenation, and the above transformation would open the way to the synthesis of biologically attractive penams.

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Experimental Part

1. *General.* Solvents: CH_2Cl_2, Et_2O, MeCN, hexane and toluene were distilled over CaH_2 and stored over molecular sieves (4Å), THF was destilled over Na, DMF, MeOH, and EtOH (*Merck*) were dried over molecular sieves (4Å). TLC: *Merck* TLC aluminum sheets, silica gel $60F_{254}$. Column chromatography (CC): silica gel *Merck 60* (0.04-0.063 mm). M.p.: *Mettler-FP5* apparatus; uncorrected. IR Spectra: *Perkin-Elmer 297* or *Perkin-Elmer 781* spectrophotometer; in $CHCl_3$ unless otherwise stated; absorptions in cm^{-1}. ^{1}H-NMR Spectra: *Bruker AC-300* (300 MHz), *Bruker AM-400* (400 MHz), and *Varian EM-390* (90 MHz) spectrometer, in $CDCl_3$ at 300 K unless otherwise stated; ´ in ppm refer to TMS (0 ppm) or residual C*H*Cl_3 (7.27 ppm) as internal standard; coupling constants *J* in Hz. ^{13}C-NMR Spectra: *Varian XL-200* (50.4 MHz) spectrometer; ´ in ppm refer to *C*DCl_3 as internal standard (77.0 ppm); signal multiplicity from DEPT spectra. MS: *Varian MAT-711*, *Varian MAT-112*, *Finnigan MAT-90*, *Finnigan SSQ-700*, or *Finningan TSQ-700* mass spectrometers; EI-mode: direct injection, 70 eV; CI-mode: with 2-methylpropane or NH_3; *m/z* (rel. %).

2. *Acid Chloride/Imine Cycloaddition. – General Procedure 1 (GP 1).* Into a soln. of imine (4,5-dihydro-1,3-thiazole **2** or benzalaniline **11**; 5 mmol) and Et_3N (1.01 g, 10 mmol) in CH_2Cl_2 (50 ml) at r.t., a soln. of acid chloride **3** (10 mmol) in CH_2Cl_2 (2 ml) was added within 1 h. After stirring for 1 d, 505 mg (5 mmol) of Et_3N was added in one portion, and additional **3** (5 mmol) was added dropwise within 1 h. The mixture was maintained at r.t. for another 2–3 d, and then filtered through a silica gel column. The filtrate was washed with 2N HCl, 5% $NaHCO_3$, and brine, subsequently. After removal of the solvent *i.v.*, the residue was either chromatographed or recrystallized.

General Procedure 2 (GP 2). A soln. of imine (**2** or **11**; 1 mmol) and acid chloride **3** (1.2 mmol) in hexane (15 ml) was heated at reflux for 3 h. Then, a soln. of Et_3N (3 mmol) in hexane (1 ml) was added within 1 h and the mixture maintained at reflux for another 3 h. After addition of Et_2O (30 ml), the mixture was filtered through a short silica gel column, the filtrate concentrated *i.v.*, and the residue chromatographed or recrystallized.

2.1. *Formation of Bicyclic β-Lactams*. 2.1.1. *6*-exo-*Acetoxy-2,2-dimethyl-3*-endo-*methylsulfanyl-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptan-7-one* (**6a**) and *6*-exo-*acetoxy-2,2-dimethyl-3*-exo-*methylsulfanyl-5-phenyl-4-thia-1-azabicyclo[3.2.0]-heptan-7-one* (**6a'**). According to *GP 1*, with 4,5-dihydro-4,4-dimethyl-5-methylsulfanyl-2-phenyl-1,3-thiazole [9a] (**2a**; 762 mg, 3.215 mmol), Et_3N (1.30 g, 12.86 mmol), and acetoxyacetyl chloride (**3b**, 1.754 mg, 12.86 mmol), after CC with hexane/Et_2O (10:1), 672 mg (62%) of **6a/6a'** were obtained as a 2:1 mixture of diastereoisomers. After prep. TLC with hexane/Et_2O (4:1, 4× developing), **6a** and **6a'** were isolated in pure form. **6a**: White crystals. M.p. 126–128°. IR: 2985*w*, 2920*w*, 1785*s*, 1755*s*, 1450*w*, 1390*w*, 1370*m*, 1275*m*, 1255*w*, 1235*m*, 1180*m*, 1160*w*, 1125*m*, 1060*w*, 1025*w*, 915*w*, 700*m*. ^{1}H-NMR: 7.35–7.3 (*m*, 5 arom. H); 6.02 (*s*, HC(6)); 4.55 (*s*, HC(3)); 2.26 (*s*, MeS); 1.94 (*s*, *endo*-MeC(3)); 1.64 (*s*, MeCO); 1.29 (*s*, *exo*-MeC(3)). ^{13}C-NMR: 167.9 (*s*, C(7)); 167.8 (*s*, Me*C*O); 136.9 (*s*, 1 arom. C); 128.1, 127.8, 126.2 (3*d*, 5 arom. CH); 84.4 (*d*, C(6)); 80.5 (*s*, C(5)); 72.7 (*d*, C(3)); 70.5 (*s*, C(2)); 27.5, 21.3 (2*q*, *Me*$_2$C); 19.5 (*q*, *Me*CO); 16.6 (*q*, MeS). CI-MS: 340 (12), 339 (20), 338 (100, $[M + 1]^+$), 290 (17), 238 (17). Anal. calc. for $C_{16}H_{19}NO_3S_2$ (337.46): C 56.95, H 5.68, N 4.15, S 19.00; found: C 56.91, H 5.49, N 4.37, S 19.28.

Suitable crystals for the X-ray crystal-structure determination were grown from hexane/Et_2O by slow evaporation of the solvent at r.t.

6a': White crystals. M.p. 100.5–101.5°. IR: 2990*w*, 2920*w*, 1770*s*, 1760*s*, 1450*w*, 1390*w*, 1370*m*, 1275*m*, 1250*m*, 1240*m*, 1185*m*, 1120*m*, 1050*w*, 1030*m*, 920*w*, 700*m*. ^{1}H-NMR: 7.35–7.3 (*m*, 5 arom. H); 5.90 (*s*, HC(6)); 4.62 (*s*, HC(3)); 2.28 (*s*, MeS); 1.87 (*s*, *endo*-MeC(3)); 1.63 (*s*, MeCO); 1.10 (*s*, *exo*-MeC(3)). ^{13}C-NMR: 168.5 (*s*, Me*C*O); 167.7 (*s*, C(7)); 137.0 (*s*, 1 arom. C); 128.2, 127.7, 126.3 (3*d*, 5 arom. CH); 85.3 (*d*, C(6)); 79.0 (*s*, C(5)); 70.7 (*d*, C(3)); 68.9 (*s*, C(2)); 22.2, 22.0 (2*q*, *Me*$_2$C); 19.5 (*q*, *Me*CO); 17.3 (*q*, MeS). CI-MS: 340 (11), 339 (19), 338 (100, [*M* + 1]$^{+}$), 304 (19), 290 (16), 280 (16), 278 (10), 238 (35), 234 (26), 188 (7), 178 (7). Anal. calc. for $C_{16}H_{19}NO_3S_2$ (337.46): C 56.95, H 5.68, N 4.15, S 19.00; found: C 57.11, H 5.48, N 4.19, S 18.88.

2.1.2. *2,2-Dimethyl-3-*endo/exo-*methylsulfanyl-5-phenyl-6-*exo-*phthalimido-4-thia-1-azabicyclo[3.2.0]heptan-7-one* (**6b**). According to *GP 2*, with **2a** (119 mg, 0.5 mmol), phthalimidoacetyl chloride (**3c**, 134 mg, 0.6 mmol), and Et_3N (152 mg, 1.5 mmol). After prep. TLC with hexane/Et_2O (10:1): 31 mg (15%) of **6b** as a mixture of 2 diastereoisomers. White crystals. M.p. 88°. IR: 3030*w*, 3000*w*, 2980*w*, 2930*w*, 1790*s*, 1775*s*, 1725*s*, 1385*s*, 1270*m*, 1250*m*, 1110*m*, 965*w*, 710*w*, 700*w*. ^{1}H-NMR (2 diastereoisomers, 1:3): 7.65–7.05 (*m*, 9 arom. H); 5.84, 5.67 (2*s*, HC(6)); 4.67, 4.60 (2*s*, HC(3)); 2.30 (*s*, MeS); 2.06, 1.99, 1.45, 1.26 (4*s*, Me_2C). ^{13}C-NMR (2 diastereoisomers, 1:3): 168.0 (*s*, C(7)); 167.3 (*s*, 2 C=O); 137.3, 130.9 (2*s*, 3 arom. C); 134.1, 128.00, 127.97, 127.8, 125.5, 123.3 (6*d*, 9 arom. C); 79.4 (*s*, C(5)); 73.1, 70.4 (2*d*, C(6)); 71.1, 69.6 (2*s*, C(2)); 69.2, 68.3 (2*d*, C(3)); 28.3, 22.5, 21.6, 22.3 (4*q*, *Me*$_2$C); 17.4, 16.8 (2*q*, MeS). CI-MS: 425 (11, [*M* + 1]$^{+}$), 260 (16), 259 (100), 238 (21), 145 (5), 72 (5). Anal. calc. for $C_{22}H_{20}N_2O_3S_2$ (424.54): C 62.24, H 4.75, N 6.60, S 15.11; found: C 62.12, H 4.66, N 6.39, S 15.35.

2.2. *Formation of Monocyclic β-Lactams*. 2.2.1. *3-Acetoxy-1,4-diphenyl-2-azetidinone* (**12a**) [23a,b]. According to *GP 1*, with **3b** (2.048 g, 15 mmol) and benzalaniline (**11**, 0.905 g, 5 mmol), CC with hexane/Et_2O (12:1): 1.299 g (92%) of **12a** (2 diastereoisomers). White crystals. M.p. 138–139°. IR: 1765*s*, 1760*s*, 1600*w*, 1500*m*, 1390*m*, 1380*m*, 1240*m*, 1145*m*, 1100*w*, 700*m*. ^{1}H-NMR (2 diastereoisomers, 1:1): 7.45–7.25 (*m*, 9 arom. H); 7.15–7.05 (*m*, 1 arom. H); 5.97, 5.41 (2*d*, *J* = 4.9 and 1.7, resp., HC(3)); 5.40, 4.96 (2*d*, *J* = 4.9 and 1.7, resp., HC(4)); 2.21, 1.69 (2*s*, Me). ^{13}C-NMR (2 diastereoisomers, 1:1): 169.6, 161.7 (2*s*, 2 C=O); 136.8–117.4 (12 arom. C); 82.4, 76.2 (2*d*, C(3)); 63.6, 61.3 (2*d*, C(4)); 20.4, 19.7 (2*q*, Me). CI-MS: 283 (19), 282 (100, $[M + 1]^+$), 234 (9), 224 (8), 222 (10), 195 (11), 183 (10), 182 (60), 163 (12), 147 (19), 133 (7), 101 (15), 94 (47), 93 (9). Anal. calc. for C_{17} $H_{15}NO_3$ (281.32): C 72.58, H 5.37, N 4.98; found: C 72.55, H 5.15, N 5.17.

2.2.2. *3,4*-trans-*1,4-Diphenyl-3-phthalimido-2-azetidinone* (**12b**) [23d,e]. According to *GP 1*, with **3c** (3.353 g, 15 mmol) and **11** (0.905 g, 5 mmol), recrystallization from Et_2O/CH_2Cl_2/hexane: 1.068 g (58%) of **12b**. White crystals. M.p. 224–225° ([23d]: 224–230°). IR: 1765*m*, 1725*s*, 1600*w*, 1500*m*, 1390*m*, 1150*w*, 1105*w*, 1090*w*, 970*w*, 715*w*, 700*w*. ^{1}H-NMR (400 MHz): 7.9–7.85 (*m*, 2 arom. H); 7.8–7.75 (*m*, 2 arom. H); 7.4–7.25 (*m*, 9 arom. H); 7.1–7.05 (*m*, 1 arom. H); 5.40 (*d*, *J* = 2.7, HC(3)); 5.30 (*d*, *J* = 2.7, HC(4)). ^{13}C-NMR: 166.7 (*s*, 2 C=O); 162.0 (*s*, C(2)); 137.1–117.6 (18 arom. C); 62.7 (*d*, C(3)); 61.2 (*d*, C(4)). CI-MS: 387 (16), 386 (100, $[M + NH_4]^+$), 369 (25, $[M + 1]^+$), 366 (14). Anal. calc. for $C_{23}H_{16}N_2O_3$ (368.40): C 74.99, H 4.38, N 7.60; found: C 74.78, H 4.66, N 7.63.

3. *Reactions of Acid Chlorides with 4,5-Dihydro-1,3-thiazoles* **2b** *and* **2c**. – 3.1. *2-Benzylidene-3-dichloroacetyl-4,4-dimethyl-5-methylsulfanyl-1,3-thiazolidine* (**7a**) and *2,3,6,7-Tetrahydro-6,6-dichloro-7-dichloromethyl-7-hydroxy-3,3-dimethyl-2-*

*methylsulfanyl-8-phenyl-5*H*-pyrido[2,1-*b*][1,3]thiazol-5-one* (**8**). a) According to *GP 1*, with **2b** (147 mg, 0.586 mmol), Et_3N (237 mg, 2.35 mmol), and **3a** (348 mg, 2.35 mmol), CC with hexane/Et_2O (10:1): 114 mg (53%) of **7a** and 130 mg (47%) of **8** (mixture of 2 diastereoisomers). **7a**: Brown crystals. M.p. 97–99°. IR: 2960*s*, 2920*s*, 2860*s*, 1700*s*, 1600*w*, 1460*w*, 1375*m*, 1355*m*, 1340*m*, 1255*w*, 1170*w*. ^{1}H-NMR: 7.35–7.3 (*m*, 5 arom. H); 6.64 (*s*, PhC*H*=C); 6.11 (*s*, Cl_2CH); 4.35 (*s*, HC(5)); 2.21 (*s*, MeS); 1.59, 1.47 (2*s*, Me_2C). ^{13}C-NMR: 163.9 (*s*, C=O); 136.4 (*s*, C(2)); 134.7 (*s*, 1 arom. C); 128.6, 127.9, 127.2 (3*d*, 5 arom. CH); 113.4 (*d*, Ph*C*H=C); 67.6 (*s*, C(4)); 65.2 (*d*, Cl_2CH); 64.3 (*d*, C(5)); 24.3, 20.5 (2*q*, *Me*$_2$C); 16.0 (*q*, MeS). CI-MS: 366 (2), 364 (8), 362 (11, $[M + 1]^+$), 252 (57), 236 (6), 206 (5), 205 (15), 204 (100), 191 (10), 135 (14). Anal. calc. for $C_{15}H_{17}Cl_2NOS_2$ (362.34): C 49.72, H 4.73, Cl 19.57, N 3.87, S 17.70; found: C 50.00, H 5.00, Cl 19.65, N 3.72, S 17.51.

8: Yellow oil. IR: 3540*m*, 3020*w*, 3000*m*, 2980*m*, 2920*w*, 1720*s*, 1710*s*, 1630*s*, 1510*m*, 1385*s*, 1370*s*, 1360*s*, 1310*m*, 1280*m*, 1250*m*, 1170*m*, 1125*s*, 1040*m*, 1020*m*, 910*m*, 850*m*, 810*m*, 700*m*, 650*m*. ^{1}H-NMR (2 diastereoisomers, 1:1): 7.5–7.4 (*m*, 5 arom. H); 6.20, 6.18 (2*s*, Cl_2CH); 4.24, 4.21 (2*s*, HC(2)); 3.22, 3.17 (2*s*, OH); 2.20, 2.14 (2*s*, MeS); 1.81, 1.74, 1.73, 1.55 (4*s*, Me_2C). ^{13}C-NMR (2 diastereoisomers, 1:1): 159.5 (*s*, C=O); 139.9 (*s*, C(8a)); 135.5, 135.1 (2*s*, 1 arom. C); 131.4, 131.3, 128.7, 128.6, 128.56, 128.5 (6*d*, 5 arom. CH); 128.8, 128.7 (2*s*, C(8)); 106.3, 105.0 (2*s*, C(7)); 81.8, 81.6 (2*s*, C(6)); 76.3, 76.2 (2*d*, Cl_2CH); 72.1, 71.8 (2*s*, C(3)); 62.0, 61.8 (2*d*, C(2)); 25.2, 24.3, 21.8, 19.0 (4*q*, *Me*$_2$C); 16.5, 14.9 (2*q*, MeS). CI-MS: 478 (13), 476 (53), 474 (100), 472 (76, $[M + 1]^+$), 456 (6), 447 (8), 442 (7), 440 (16), 439 (6), 438 (34), 436 (35), 428 (12), 426 (24), 424 (21), 422 (14), 420 (13), 402 (13), 400 (27), 398 (20), 396 (15), 364 (8), 362 (6), 354 (6).

b) Into a soln. of **7a** (66 mg, 0.18 mmol) and Et_3N (55 mg, 0.54 mmol) in hexane (5 ml), 32 mg (0.22 mmol) of **3a** were added dropwise. The mixture was heated at reflux for 4 h. After removal of the solvent *i.v.*, the residue was chromatographed with hexane/Et_2O (10:1), furnishing 26 mg (31%) of **8**.

3.2. *(E)-2-(3,3-Dichloro-2-oxo-1-phenylpropylidene)-4,4-dimethyl-5-(methylthio)-1,3-thiazolidine* (**9**). a) According to *GP 2*, with **2b** (301 mg, 1.2 mmol), **3a** (195 mg, 1.32 mmol), and Et_3N (303 mg, 3 mmol), CC with hexane/Et_2O (10:1): 159 mg (37%) of **7a** and 195 mg (45%) of **9**: White crystals. M.p. 138.5–140°. IR (KBr): 2950*m*, 1600*s*, 1510*s*, 1505*s*, 1380*s*, 1370*s*, 1330*m*, 1260*m*, 1165*m*, 1135*m*, 980*w*, 820*m*, 800*m*, 770*m*, 705*m*, 695*m*, 650*m*. ^{1}H-NMR: 10.92 (*s*, NH); 7.6–7.25 (*m*, 5 arom. H); 5.91 (*s*, Cl_2CH); 4.39 (*s*, HC(5)); 2.17 (*s*, MeS); 1.57 (*s*, Me_2C). ^{13}C-NMR: 179.5 (*s*, C=O); 170.8 (*s*, C(2)); 136.2 (*s*, 1 arom. C); 131.8, 129.0, 128.4 (3*d*, 5 arom. CH); 100.4 (*s*, Ph*C*=C); 69.1 (*s*, C(4)); 68.0 (*d*, Cl_2CH); 63.2 (*d*, C(5)); 27.5, 23.3 (2*q*, *Me*$_2$C); 15.5 (*q*, MeS). CI-MS: 366 (17), 365 (13), 364 (74), 363 (20), 362 (100, $[M + 1]^+$), 330 (7), 328 (7). Anal. calc. for $C_{15}H_{17}Cl_2NOS_2$ (362.34): C 49.72, H 4.73, Cl 19.57, N 3.87, S 17.70; found: C 49.50, H 4.48, Cl 19.77, N 3.99, S 17.40.

Suitable crystals for the X-ray crystal-structure determination were grown from hexane/Et_2O by slow evaporation of the solvent.

b) Into a soln. of **2b** (189 mg, 0.75 mmol) in hexane (10 ml), **3a** (167 mg, 1.13 mmol) was added. The mixture was heated under reflux for 3 h. After addition of Et_2O (30 ml), the mixture was filtered through a short silica gel column, and the filtrate concentrated *i.v.* After CC with hexane/Et_2O (10:1), 43 mg (16%) of **7a** and 174 mg (64%) of **9** were obtained.

3.3. *(Z)-3-(Acetoxyacetyl)-2-benzylidene-4,4-dimethyl-5-methylsulfanyl-1,3-thiazolidine* (**7b**). According to *GP 2*, with **2b** (228 mg, 0.908 mmol), **3b** (248 mg,

1.817 mmol), and Et_3N (367 mg, 3.63 mmol), CC with hexane/Et_2O (10:1): 112 mg (35%) of **7b**. White crystals. M.p. 87–88.5°. IR: 3005*w*, 2920*w*, 1745*s*, 1680*s*, 1610*w*, 1490*w*, 1445*w*, 1420*w*, 1385*s*, 1370*m*, 1315*m*, 1240*m*, 1170*m*, 1070*m*, 910*m*, 695*m*. ^{1}H-NMR: 7.4–7.35 (*m*, 5 arom. H); 6.32 (*s*, PhC*H*=C); 4.93 (*s*, CH_2); 4.37 (*s*, HC(5)); 2.26 (*s*, MeCO); 2.17 (*s*, MeS); 1.68, 1.53 (2*s*, Me_2C). ^{13}C-NMR: 170.3 (*s*, Me*C*O); 166.5 (*s*, C=O); 135.7 (*s*, C(2)); 135.2 (*s*, 1 arom. C); 128.4, 127.8, 126.8 (3*d*, 5 arom. CH); 114.5 (*d*, Ph*C*H=C); 67.4 (*s*, C(4)); 64.5 (*d*, C(5)); 63.3 (*t*, CH_2); 24.9 (*q*, *Me*CO); 21.0, 20.4 (2*q*, *Me*$_2$C); 16.0 (*q*, MeS). CI-MS: 354 (12), 353 (21), 352 (100, $[M + 1]^+$), 351 (11), 304 (7). Anal. calc. for $C_{17}H_{21}NO_3S_2$ (351.49): C 58.09, H 6.02, N 3.99, S 18.24; found: C 58.22, H 5.91, N 4.02, S 18.03.

Suitable crystals for the X-ray crystal-structure determination were grown from hexane/Et_2O by slow evaporation of the solvent.

3.4. *2-Benzylidene-4,4-dimethyl-5-methylsulfanyl-3-(phthalimidoacetyl)-1,3-thiazolidine* (**7c**). According to *GP 2*, with **2b** (69 mg, 0.275 mmol), **3c** (74 mg, 0.33 mmol), and Et_3N (83 mg, 0.82 mmol), CC with hexane/Et_2O (8:1): 30 mg (25%) of **7c**. Pale yellow powder. M.p. 55–56°. IR (KBr): 2920*w*, 1770*w*, 1720*s*, 1680*m*, 1610*w*, 1420*m*, 1390*m*, 1370*m*, 1290*w*, 1270*w*, 1230*w*, 1110*w*, 955*w*, 750*w*, 715*w*, 695*w*. ^{1}H-NMR: 7.9–7.85 (*m*, 2 arom. H); 7.75–7.7 (*m*, 2 arom. H); 7.4–7.25 (*m*, 5 arom. H); 6.57 (*s*, CH=C); 4.84, 4.76 (*AB*, *J* = 16.4, CH_2); 4.41 (*s*, HC(5)); 2.29 (*s*, MeS); 1.68, 1.52 (2*s*, Me_2C). ^{13}C-NMR: 167.6, 165.7 (2*s*, 3 C=O); 135.7 (*s*, C(2)); 135.2, 131.9 (2*s*, 3 arom. C); 133.9, 128.4, 127.9, 126.8, 123.3 (5*d*, 9 arom. CH); 115.5 (*d*, *C*H=C); 67.7 (*s*, C(4)); 64.4 (*d*, C(5)); 41.7 (*t*, CH_2); 24.9, 21.0 (2*q*, *Me*$_2$C); 15.9 (*q*, MeS). CI-MS: 441 (12), 440 (28), 439 (100, $[M + 1^+]$), 391 (5). Anal. calc. for $C_{23}H_{22}N_2O_3S_2$ (438.57): C 62.99, H 5.06, N 6.39, S 14.62; found: C 63.18, H 5.32, N 6.34, S 14.41.

3.5. *3-Dichloroacetyl-2-(3,3-dichloro-2-oxopropylidene)-4,4-dimethyl-5-methylsulfanyl-1,3-thiazolidine* (**10**). According to *GP 2*, with 4,5-dihydro-2,4,4-trimethyl-5-methylsulfanyl-1,3-thiazole (**2c**; 175 mg, 1 mmol), **3a** (178 mg, 1.2 mmol), and Et_3N (251 mg, 2.5 mmol), CC with hexane/Et_2O (10:1): 53 mg (19%) of **10**. Yellow oil. IR: 3200*w*, 3000*m*, 2980*m*, 2920*m*, 1725*s*, 1660*m*, 1595*m*, 1530*s*, 1515*s*, 1505*s*, 1390*m*, 1370*m*, 1320*s*, 1270*m*, 1160*s*, 1120*m*, 810*m*. ^{1}H-NMR: 6.52 (*s*, CH=C); 6.27, 5.90 (2*s*, 2 Cl_2CH); 4.29 (*s*, HC(5)); 2.29 (*s*, MeS); 1.65, 1.59 (2*s*, Me_2C). ^{13}C-NMR: 184.7, 165.7 (2*s*, 2 C=O); 163.2 (*s*, C(2)); 96.1 (*d*, *C*H=C); 71.6 (*s*, C(4)); 69.5, 64.5 (2*d*, 2 Cl_2CH); 62.1 (*d*, C(5)); 24.0, 20.4 (2*q*, *Me*$_2$C); 15.8 (*q*, MeS). CI-MS: 402 (8), 400 (28), 399 (9), 398 (49), 397 (9), 396 (35, $[M + 1]^+$), 312 (5), 290 (13), 289 (9), 288 (69), 287 (14), 286 (100), 202 (6).

4. *Hydrolysis of 3-Acetoxy-2-azetidinone* **12a** *and 6-Acetoxypenam* **6a**. – 4.1. trans-*3-Hydroxy-1,4-diphenyl-2-azetidinone* (*trans*-**13**) and cis-*3-hydroxy-1,4-diphenyl-2-azetidinone* (*cis*-**13**). Into a soln. of **12a** (410 mg, 1.46 mmol) in MeOH (50 ml) at 0°, a soln. of sat. aq. $NaHCO_3$ (2 ml) was added. The mixture was maintained at 0° for 30 min. Then, AcOEt (200 ml) and H_2O (80 ml) were added. The org. phase was separated, and the aq. phase was extracted with AcOEt (3 x 120 ml). The combined org. phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *i.v.* After CC of the residue with hexane/Et_2O (8:1), afforded 153 mg (44%) of *trans*-**13** and 151 mg (43%) of *cis*-**12**. *trans*-**13** [25b]: White crystals. M.p. 181–183° ([25b]: 180–181°). IR: 3350*w*, 1750*s*, 1600*w*, 1505*m*, 1385*m*, 1140*w*. ^{1}H-NMR: 7.4–7.2 (*m*, 9 arom. H); 7.1–7.05 (*m*, 1 arom. H); 4.92 (*d*, *J* = 1.8, HC(4)); 4.76 (*dd*, *J* = 1.8, 6.2, HC(2)); 3.49 (*d*, *J* = 6.2, OH). ^{13}C-NMR ((D$_5$)Py): 168.0 (*s*, C=O); 138.3, 137.9 (2*s*, 2 arom. C); 129.6, 128.8, 126.6, 124.3, 117.9 (5*d*, 10 arom. CH); 85.5 (*d*, C(3)); 66.6 (*d*, C(4)). CI-MS: 258 (16), 257 (100, $[M + NH_4]^+$), 241 (16), 240

(100, $[M + 1]^+$). Anal. calc. for $C_{15}H_{13}NO_2$ (239.28): C 75.30, H 5.48, N 5.85; found: C 75.42, H 5.27, N 6.00.

cis-**13** [25b]: White crystals. M.p. 199–201° ([25b]: 206–207°). IR: 3600*w*, 3000*w*, 1750*s*, 1600*w*, 1500*m*, 1455*w*, 1385*m*, 1265*m*, 1150*w*, 1115*m*, 700*m*. ^{1}H-NMR: 7.45–7.25 (*m*, 9 arom. H); 7.15–7.05 (*m*, 1 arom. H); 5.33 (*d*, *J* = 5.4, HC(4)); 5.21 (*dd*, *J* = 5.4, 9.2, HC(3)); 2.21 (*d*, *J* = 9.2, OH). ^{13}C-NMR ((D$_5$)Py): 168.3 (*s*, C=O); 138.6, 135.7 (2*s*, 2 arom. C); 129.6, 128.9, 128.6, 128.4, 124.3, 117.8 (6*d*, 10 arom. CH); 78.6 (*d*, C(3)); 63.3 (*d*, C(4)). CI-MS: 258 (17), 257 (100, $[M + NH_4]^+$), 241 (5), 240 (30, $[M + 1]^+$), 58(5). Anal. calc. for $C_{15}H_{13}NO_2$ (239.28): C 75.30, H 5.48, N 5.85; found: C 75.51, H 5.27, N 5.97.

4.2. *6*-exo-*Hydroxy-2,2-dimethyl-3*-endo-*methylsulfanyl-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptan-7-one* (*endo*-**16**) and *6*-exo-*hydroxy-2,2-dimethyl-3*-exo-*methylsulfanyl-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptan-7-one* (*exo*-**16**). In analogy to experiment 4.1, the reaction of **6a** (460 mg, 1.36 mmol) with sat. $NaHCO_3$ (3 ml) at 0° for 1 h afforded, after CC with hexane/Et_2O (5:1), 307 mg (76%) of **16** as a mixture of 2 diastereoisomers. After prep. TLC with hexane/Et_2O (4:1), *endo*- and *exo*-**16** were isolated in pure form. *endo*-**16**: White crystals. M.p. 103.5–104.5°. IR: 3560*m*, 3380*m*, 3000*m*, 2980*m*, 2920*m*, 1760*s*, 1600*w*, 1480*w*, 1460*w*, 1445*m*, 1390*m*, 1370*m*, 1280*s*, 1210*s*, 1180*s*, 1150*s*, 1060*m*, 1030*m*, 1005*m*, 980*m*, 870*m*, 850*m*, 700*s*, 640*m*. ^{1}H-NMR: 7.45–7.35 (*m*, 5 arom. H); 5.22 (*d*, *J* = 9.6, HC(6)); 4.54 (*s*, HC(3)); 2.32 (*d*, *J* = 9.6, OH); 2.24 (*s*, MeS); 1.91, 1.32 (2*s*, Me_2C). ^{13}C-NMR: 173.3 (*s*, C=O); 138.1 (*s*, 1 arom. C); 128.3, 128.1, 126.2 (3*d*, 5 arom. CH); 86.9 (*d*, C(6)); 81.7 (*s*, C(5)); 72.8 (*d*, C(3)); 69.9 (*s*, C(2)); 27.8, 21.3 (2*q*, *Me*$_2$C); 16.7 (*q*, MeS). CI-MS: 296 (25, $[M + 1]^+$), 240 (9), 239 (14), 238 (100). Anal. calc. for $C_{14}H_{17}NO_2S_2$ (295.43): C 56.92, H 5.80, N 4.74, S 21.71; found: C 56.64, H 5.79, N 4.54, S 21.50.

exo-**16**: White crystals. M.p. 141.5–142.7°. IR: 3560*w*, 3330*w*, 2980*m*, 2920*w*, 1760*s*, 1450*m*, 1390*m*, 1370*m*, 1290*m*, 1260*m*, 1170*m*, 1145*m*, 700*m*. ^{1}H-NMR: 7.45–7.35 (*m*, 5 arom. H); 5.07 (*d*, *J* = 9.6, HC(6)); 4.54 (*s*, HC(3)); 2.27 (*s*, MeS); 2.14 (*d*, *J* = 9.6, OH); 1.85, 1.13 (2*s*, Me_2C). ^{13}C-NMR ($(CD_3)_2CO$): 172.2 (*s*, C=O); 139.8 (*s*, 1 arom. C); 128.3, 128.1, 126.9 (3*d*, 5 arom. CH); 89.6 (*d*, C(6)); 80.9 (*s*, C(5)); 70.4 (*d*, C(3)); 68.8 (*s*, C(2)); 22.4, 22.3 (2*q*, *Me*$_2$C); 17.0 (*q*, MeS). CI-MS: 313 (100, $[M + NH_4]^+$), 296 (25, $[M + 1]^+$), 284 (18), 283 (14), 269 (17), 267 (25), 238 (43).

Suitable crystals of *exo*-**16** for the X-ray crystal-structure determination were grown from CH_2Cl_2/Et_2O/hexane by slow evaporation of the solvent.

5. *Sulfonylation of 3-Hydroxy-2-azetidinones* **13** *and 6-Hydroxypenams* **16**. – 5.1. trans-*3-{[(4-Chlorophenyl)sulfonyl]oxy}-1,4-diphenyl-2-azetidinone* (*trans*-**14**). Into a soln. of *trans*-**13** (190 mg, 0.795 mmol) in CH_2Cl_2 at 0°, *Hünig*'s base (103 mg, 0.80 mmol) was added. After stirring for 10 min, a soln. of (4-chlorobenzene)sulfonyl chloride (252 mg, 1.19 mmol) in CH_2Cl_2 (2 ml) was added dropwise. The mixture was stirred overnight allowing the temp. to rise to r.t. Then, CH_2Cl_2 (50 ml) was added. The org. phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *i.v.* Crystallization of the residue (CH_2Cl_2/Et_2O/hexane) furnished 296 mg (90%) of *trans*-**14**. White crystals. M.p. 187.0–187.5°. IR: 1770*s*, 1600*w*, 1590*w*, 1500*m*, 1385*s*, 1190*m*, 1185*m*, 1145*m*, 1090*m*, 1070*m*, 870*m*, 845*m*, 830*m*, 700*w*. ^{1}H-NMR: 7.85–7.8 (*m*, 2 arom. H); 7.55–7.5 (*m*, 2 arom. H); 7.45–7.35 (*m*, 3 arom. H); 7.3–7.2 (*m*, 6 arom. H); 7.15–7.05 (*m*, 1 arom. H); 5.15 (*d*, *J* = 1.6, HC(3)); 5.11 (*d*, *J* = 1.6, HC(4)). ^{13}C-NMR ((D_6)DMSO): 159.1 (*s*, C=O); 140.2, 135.8, 133.9, 133.2 (4*s*, 4 arom. C); 130.0, 129.8, 129.1, 128.9, 128.7, 126.9, 124.8, 117.6 (8*d*, 14 arom. CH); 84.7 (*d*, C(3)); 62.2 (*d*, C(4)). CI-MS: 433 (30), 432 (27), 431 (100, $[M + NH_4]^+$), 414 (12, [*M*

+ 1]$^+$). Anal. calc. for $C_{21}H_{16}ClNO_4S$ (413.88): C 60.94, H 3.90, Cl 8.57, N 3.38, S 7.75; found: C 61.10, H 4.05, Cl 8.85, N 3.37, S 7.49.

5.2. cis-*3-{[(4-Chlorophenyl)sulfonyl]oxy}-1,4-diphenyl-2-azetidinone* (*cis*-**14**). In analogy to experiment 5.1, from *cis*-**13** (160 mg, 0.67 mmol), *Hünig*'s base (203 mg, 2.35 mmol), and (4-chlorobenzene)sulfonyl chloride (495 mg, 2.35 mmol), after crystallization from CH_2Cl_2/Et_2O/hexane, 259 mg (94%) of *cis*-**14** were obtained. White crystals. M.p. 209–211°. IR: 1765*s*, 1600*w*, 1500*m*, 1385*m*, 1190*m*, 1175*m*, 1085*m*, 870*m*, 830*m*, 700*w*. ^{1}H-NMR: 7.5–7.25 (*m*, 13 arom. H); 7.15–7.05 (*m*, 1 arom. H); 5.85 (*d*, *J* = 5.0, HC(3)); 5.34 (*d*, *J* = 5.0, HC(4)). ^{13}C-NMR ((D$_6$)DMSO): 160.0 (*s*, C=O); 139.8, 136.2, 133.6, 131.9 (4*s*, 4 arom. C); 129.8, 129.2, 129.0, 128.7, 128.4, 127.8, 124.7, 117.1 (8*d*, 14 arom. C); 79.8 (*d*, C(3)); 60.2 (*d*, C(4)). EI-MS: 413 (9, M^+), 296 (25), 295 (12), 294 (67), 239 (14), 238 (86), 221 (9), 183 (15), 182 (100), 181 (31), 180 (59), 175 (22), 159 (27), 152 (11), 131 (34). Anal. calc. for $C_{21}H_{16}ClNO_4S$ (413.88): C 60.94, H 3.90, Cl 8.57, N 3.38, S 7.75; found: C 60.81, H 3.79, Cl 8.29, N 3.38, S 7.97.

5.3. *6*-exo-*{[(4-Chlorophenyl)sulfonyl]oxy}-2,2-dimethyl-3*-endo-*methylsulfanyl-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptan-7-one* (*endo*-**17a**) and *6*-exo-*{[(4-chlorophenyl)sulfonyl]oxy}-2,2-dimethyl-3*-exo-*methylsulfanyl-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptan-7-one* (*exo*-**17a**). Into a soln. of the diastereoisomeric mixture of **16** (139 mg, 0.47 mmol) in CH_2Cl_2 (5 ml) at 0°, Et_3N (95 mg, 0.94 mmol) was added. After 10 min, a soln. of (4-chlorobenzene)sulfonyl chloride (149 mg, 0.705 mmol) in CH_2Cl_2 (1 ml) was added dropwise. The mixture was maintained at r.t. overnight, then, CH_2Cl_2 (30 ml) was added. The soln. was washed with brine, dried (Na_2SO_4), filtered, and concentrated *i.v.* The residue, after purification by CC with hexane/Et_2O (15:1), afforded 197 mg (90%) of **17** as a 2:1 mixture of

diastereoisomers. After prep. TLC, *endo*-**17a** and *exo*-**17a** were isolated in pure form. *endo*-**17a**: White crystals. M.p. 122–123°. IR: 1785*s*, 1590*w*, 1480*w*, 1385*m*, 1270*m*, 1190*m*, 1180*m*, 1090*m*, 990*w*, 890*m*, 825*m*, 700*m*, 650*m*. ^{1}H-NMR: 7.5–7.3 (*m*, 9 arom. H); 5.84 (*s*, HC(6)); 4.53 (*s*, HC(3)); 2.26 (*s*, MeS); 1.89 (*s*, *endo*-MeC(2)); 1.20 (*s*, *exo*-MeC(2)). ^{13}C-NMR: 166.4 (*s*, C=O); 140.7, 136.6, 134.1 (3*s*, 3 arom. C); 129.4, 129.0, 128.5, 128.1, 126.4 (5*d*, 9 arom. CH); 87.4 (*d*, C(6)); 80.6 (*s*, C(5)); 72.9 (*d*, C(3)); 70.8 (*s*, C(2)); 27.3, 21.3 (2*q*, *Me*$_2$C); 16.7 (*q*, MeS). CI-MS: 487 (7), 472 (9), 470 (19, $[M + 1]^+$), 240 (9), 239 (14), 238 (100), 145 (6). Anal. calc. for $C_{20}H_{20}ClNO_4S_3$ (470.03): C 51.11, H 4.29, N 2.98, S 20.46; found: C 51.40, H 4.10, N 3.07, S 20.93.

exo-**17a**: White crystals. M.p. 131.5–132.7°. IR: 2980*m*, 2930*w*, 1785*s*, 1590*m*, 1480*m*, 1450*m*, 1400*m*, 1390*m*, 1375*m*, 1275*m*, 1260*m*, 1190*s*, 1180*m*, 1090*s*, 1050*m*, 1000*m*, 895*m*, 825*m*, 700*m*, 650*m*, 625*m*. ^{1}H-NMR: 7.5–7.25 (*m*, 9 arom. H); 5.71 (*s*, HC(6)); 4.57 (*s*, HC(3)); 2.27 (*s*, MeS); 1.81 (*s*, *endo*-MeC(2)); 1.01 (*s*, *exo*-MeC(2)). ^{13}C-NMR: 165.1 (*s*, C=O); 140.7, 136.1, 134.0 (3*s*, 3 arom. C); 129.4, 129.0, 128.5, 127.9, 126.5 (5*d*, 9 arom. CH); 88.2 (*d*, C(6)); 79.1 (*s*, C(5)); 70.9 (*d*, C(3)); 69.1 (*s*, C(2)); 25.3, 22.1 (2*q*, *Me*$_2$C); 17.3 (*q*, MeS). CI-MS: 491 (6), 490 (10), 489 (48), 488 (23), 487 (100, $[M + NH_4]^+$), 472 (5), 470 (11, $[M + 1]^+$).

5.4. *2,2-Dimethyl-3*-endo/exo-*methylsulfanyl-6*-exo-*{[(2,4-dinitrophenyl)sulfonyl]oxy}-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptan-7-one* (**17b**). In analogy to experiment 5.3, from **16** (2:1 mixture of 3-*endo* and 3-*exo* isomers; 267 mg, 0.9 mmol), and (2,4-dinitrobenzene)sulfonyl chloride (360 mg, 1.35 mmol), 410 mg (87%) of **17b** were obtained as a 2:1 mixture of diastereoisomers. Pale yellow foam. M.p. 55–57°. IR: 3090*w*, 3030*w*, 3010*w*, 2920*w*, 1785*s*, 1610*w*, 1560*s*, 1545*s*, 1450*w*, 1410*m*, 1390*m*, 1375*m*, 1350*s*, 1270*w*, 1190*s*, 1090*m*, 1050*w*, 1000*w*, 980*m*,

890*m*, 830*m*, 700*m*, 645*m*, 620*m*. ^{1}H-NMR (3-*endo*/3-*exo* isomers, 2:1): 8.6–8.55 (*m*, 1 arom. H); 8.5–8.4 (*m*, 1 arom. H); 8.15–8.0 (*m*, 1 arom. H); 7.45–7.15 (*m*, 5 arom. H); 5.98, 5.90 (2*s*, HC(6)); 4.62, 4.55 (2*s*, HC(3)); 2.28, 2.27 (2*s*, MeS); 1.89, 1.82, 1.23, 1.03 (4*s*, Me_2C). ^{13}C-NMR: 165.5, 164.2 (2*s*, C=O); 150.3, 147.8, 147.7, 136.2, 135.8, 134.6, 134.4 (7*s*, 4 arom. C); 132.7, 132.6, 128.7, 128.5, 128.2, 127.9, 127.8, 126.8, 126.4, 126.2, 120.1 (11*d*, 8 arom. CH); 89.8, 88.9 (2*d*, C(6)); 80.4, 78.9 (2*s*, C(5)); 72.8, 70.9 (2*s*, C(2)); 71.0, 69.2, (2*d*, C(3)); 27.2, 22.0, 21.6, 21.2 (4*q*, *Me*$_2$C); 17.3, 16.6 (2*q*, MeS). CI-MS: 545 (17), 544 (23), 543 (100, $[M + NH_4]^+$), 527 (5), 526 (10, $[M + 1]^+$), 511 (3). Anal. calc. for $C_{20}H_{19}N_3O_8S_3$ (525.58): C 45.71, H 3.64, N 7.99, S 18.30; found: C 45.86, H 3.74, N 8.18, S 18.09.

6. *Substitution Reaction of 3-{[(4-Chlorophenyl)sulfonyl]oxy}-2-azetidinones* **14** *with Azides*. – 6.1. cis-*3-Azido-1,4-diphenyl-2-azetidinone* (*cis*-**15**) [24b]. A mixture of *trans*-**14** (100 mg, 0.24 mmol) and NaN_3 (156 mg, 2.4 mmol) in DMF (5 ml) was heated to 55° for 1 d. Then, AcOEt (30 ml) and brine (10 ml) were added. The aq. phase was extracted with AcOEt (3 x 10 ml). The combined org. phase was dried (Na_2SO_4), filtered, and concentrated *i.v.* The residue, after purification by CC with hexane/Et_2O (20:1), furnished 53 mg (82%) of *cis*-**15**. White crystals. M.p. 130–131° ([24b]: 132–134°). IR: 2120*s*, 1760*s*, 1600*w*, 1500*m*, 1385*m*, 1135*m*, 700*w*. ^{1}H-NMR: 7.35–7.3 (*m*, 3 arom. H); 7.3–7.2 (*m*, 6 arom. H); 7.05–7.0 (*m*, 1 arom. H); 5.26 (*d*, *J* = 5.4, HC(3)); 4.97 (*d*, *J* = 5.4, HC(4)). ^{13}C-NMR: 161.4 (*s*, C=O); 136.0, 132.4 (2*s*, 2 arom. C); 129.1, 129.0, 128.8, 127.4, 124.7, 117.4 (6*d*, 10 arom. CH); 67.3 (*d*, C(3)); 60.6 (*d*, C(4)). CI-MS: 283 (14), 282 (100, $[M + NH_4]^+$), 265 (3, $[M + 1]^+$), 254 (31), 237 (12). Anal. calc. for $C_{15}H_{12}N_4O$ (264.29): C 68.17, H 4.58, N 21.20; found: C 68.26, H 4.38, N 20.93.

6.2. trans-*3-Azido-1,4-diphenyl-2-azetidinone* (*trans*-**15**). a) In analogy to experiment 6.1, from *cis*-**14** (166 mg, 0.4 mmol), and NaN_3 (260 mg, 4 mmol), 92 mg (87%) of *trans*-**15** were obtained. Colorless oil ([24b]: m.p. 81–83°). IR: 3060*w*, 3030*w*, 3005*w*, 2920*w*, 2115*s*, 1760*s*, 1600*s*, 1500*s*, 1490*s*, 1455*m*, 1380*s*, 1355*m*, 1330*m*, 1320*m*, 1300*m*, 1280*m*, 1260*m*, 1145*s*, 1105*w*, 1090*w*, 1080*w*, 1030*w*, 990*w*, 900*w*, 850*m*, 700*s*, 690*s*, 630*w*, 605*m*. ^{1}H-NMR: 7.45–7.25 (*m*, 9 arom. H); 7.15–7.05 (*m*, 1 arom. H); 4.88 (*d*, *J* = 2.1, HC(3)); 4.52 (*d*, *J* = 2.1, HC(4)). ^{13}C-NMR: 161.3 (*s*, C=O); 136.6, 135.2 (2*s*, 2 arom. C); 129.3, 129.2, 129.1, 125.9, 124.6, 117.4 (6*d*, 10 arom. CH); 72.3 (*d*, C(3)); 62.8 (*d*, C(4)). CI-MS: 299 (100, $[M + 1 + 2\ NH_3]^+$), 282 (73, $[M + NH_4]^+$), 271 (39), 265 (2, $[M + 1]^+$), 254 (27), 237 (8). Anal. calc. for $C_{15}H_{12}N_4O$ (264.29): C 68.17, H 4.58, N 21.20; found: C 68.18, H 4.67, N 20.95.

b) In analogy to experiment 6.1, from *cis*-**14** (83 mg, 0.2 mmol), and LiN_3 (98 mg, 2 mmol), 52 mg (98%) of *trans*-**15** were obtained.

7. *Attempted Substitution Reactions of 6-[(Arylsulfonyl)oxy]-2,2-dimethyl-3-methylsulfanyl-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptan-7-ones* (**17**). In analogy to the reaction described in *Chapter 6*, the mixture of diastereoisomers **17a** (*ca*. 0.3 mmol) and NaN_3 (*ca.* 3 mmol) in DMF (5 ml) was heated to 50–60°C. After usual workup, only starting material was recovered. Under similar conditions, reactions with **17b** and **17c** were also not successful and, in addition to starting material, significant amounts of 4,5-dihydro-4,4-dimethyl-5-methylsulfanyl-2-phenyl-1,3-thiazol (**2a**) were isolated.

8. *X-Ray Crystal Structure Determinations of* endo-**6a**, **7b**, **9**, and *exo*-**16** (see

Table and *Figs. 1 – 3*)[6]). The measurements for compounds *endo*-**6a**, **7b**, and **9** were made on a *Nicolet R3* diffractometer, those for compound *exo*-**16** on a *Rigaku AFC5R* diffractometer and a 12kW rotating anode generator, using graphite-monochromated Mo$K_{\pm}$ radiation (» = 0.71073 Å). The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. In all cases, equivalent reflections were merged. Data collection and refinement parameters are given in the *Table*. The structures were solved by direct methods using *SHELXS86* [34], which revealed the positions of all non-H atoms. The non-H atoms were refined anisotropically. In the cases of **9** and *exo*-**16**, the H-atom of the NH and OH group, respectively, were placed in the positions indicated by a difference electron density map, and their positions were allowed to refine together with an isotropic displacement parameter. All other H-atoms in all structures were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent atom (1.5 U_{eq} for the Me groups). The refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was not applied. One reflection, whose intensity was considered to be an extreme outlier, was omitted from the final refinement of the structure of *endo*-**6a**.

Neutral atom scattering factors for non-H-atoms were taken from [35a], and the scattering factors for H-atoms were taken from [36]. Anomalous dispersion effects were included in F_c [37]; the values for f' and f'' were those of [35b]. The values of the mass attenuation coefficients are those of [35c]. All calculations were performed using

[6]) CCDC-933805 – 933808 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from *The Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

the *SHELXL97* [38] program.

Table 6. *Crystallographic Data for Compounds* endo-**6a**, **7b**, **9**, *and exo*-**16**

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Legends

Fig. 1. *ORTEP Plot* [21] *of the molecular structure of* endo-**6a** (with 30% probability ellipsoids; arbitrary numbering of atoms)

Fig. 2. *ORTEP Plots* [21] *of the molecular structures of a)* **9** *and b)* **7b** (with 50% probability ellipsoids; arbitrary numbering of atoms)

Fig. 3. *ORTEP Plot* [21] *of the molecular structure of* exo-**16** (with 50% probability ellipsoids; arbitrary numbering of atoms)

Table. *Crystallographic Data for Compounds* endo-**6a**, **7b**, **9**, *and* exo-**16**

Table. *Crystallographic Data for Compounds* endo-**6a**, **7b**, **9**, *and* exo-**16**

		endo-**6a**	**7b**
Crystallized from		hexane/Et_2O	hexane/Et_2O
Empirical formula		$C_{16}H_{19}NO_3S_2$	$C_{17}H_{21}NO_3S_2$
Formula weight		337.45	351.48
Crystal color, habit		colorless, prism	colorless, prism
Crystal dimensions [mm]		0.19 × 0.43 × 0.44	0.26 × 0.37 × 0.42
Temperature [K]		297(1)	213(1)
Crystal system		monoclinic	monoclinic
Space group		$P2_1/n$	$P2_1/n$
Z		4	4
Reflections for cell determination		25	25
2θ range for cell determination [°]		30–36	30–34
Unit cell parameters	a [Å]	10.426(4)	5.9871(12)
	b [Å]	11.718(2)	18.954(4)
	c [Å]	13.928(2)	16.040(2)
	β [°]	98.50(2)	98.733(15)
	V [Å^3]	1682(1)	1799.2(6)
D_X [g cm^{-3}]		1.332	1.297
μ(MoK_α) [mm^{-1}]		0.327	0.309
Scan type		ω	ω
2θ(max) [°]		55	55
Total reflections measured		5146	4930
Symmetry independent reflections		3858	4126
Reflections with $I>2\sigma(I)$		2600	3098
Reflections used in refinement		3857	4126
Parameters refined		203	212
Final $R(F)$ [$I>2\sigma(I)$ reflections]		0.0476	0.0460
$wR(F^2)$ (all data)		0.1201	0.1085
Weighting parameters [a; b][a])		0.0499; 0.4814	0.0190; 1.2021
Goodness of fit		1.020	1.016
Final Δ_{max}/σ		0.001	0.001
$\Delta\rho$(max; min) [e Å^{-3}]		0.31; –0.20	0.62; –0.31

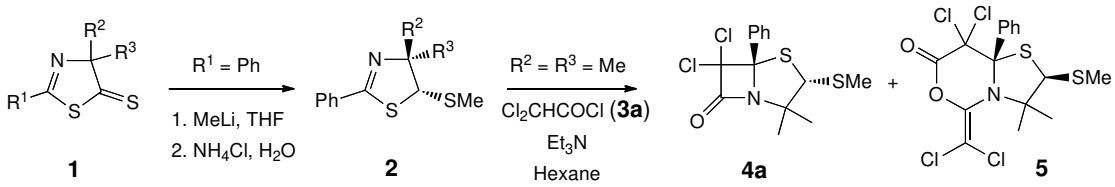
[a]) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ where $P = (F_o^2 + 2F_c^2)/3$

Table. *Crystallographic Data for Compounds* **6a**, **7b**, **9**, *and exo*-**16** (continued)

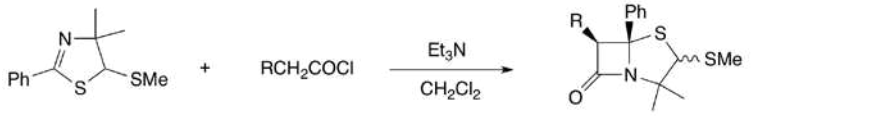
		9	*exo*-**16**
Crystallized from		hexane/Et_2O	CH_2Cl_2 /Et_2O/hexane
Empirical formula		$C_{15}H_{17}Cl_2NOS_2$	$C_{14}H_{17}NO_2S_2$
Formula weight		362.33	295.41
Crystal color, habit		colorless, prism	colorless, prism
Crystal dimensions [mm]		0.16 × 0.40 × 0.46	0.30 × 0.32 × 0.40
Temperature [K]		213(1)	173(1)
Crystal system		orthorhombic	orthorhombic
Space group		*Pbca*	*Pbcn*
Z		8	8
Reflections for cell determination		25	24
2θ range for cell determination [°]		28–32	15–22
Unit cell parameters	a [Å]	13.6699(15)	10.047(3)
	b [Å]	13.0980(15)	11.423(3)
	c [Å]	18.965(2)	24.770(4)
	β [°]	90	90
	V [Å^3]	3395.7(1)	2842(1)
D_X [g cm^{-3}]		1.417	1.380
μ(MoK_α) [mm^{-1}]		0.626	0.371
Scan type		ω	ω
2θ(max) [°]		55	60
Total reflections measured		4993	5362
Symmetry independent reflections		3907	4178
Reflections with $I>2\sigma(I)$		2472	3323
Reflections used in refinement		3907	4178
Parameters refined		197	179
Final $R(F)$ [$I>2\sigma(I)$ reflections]		0.0541	0.0348
$wR(F^2)$ (all data)		0.1263	0.0983
Weighting parameters [a; b][a])		0.0419; 4.0593	0.0477; 0.6891
Goodness of fit		1.006	1.038
Final Δ_{max}/σ		0.001	0.001
$\Delta\rho$(max; min) [e Å^{-3}]		0.57; –0.28	0.43; –0.19

[a]) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ where $P = (F_o^2 + 2F_c^2)/3$

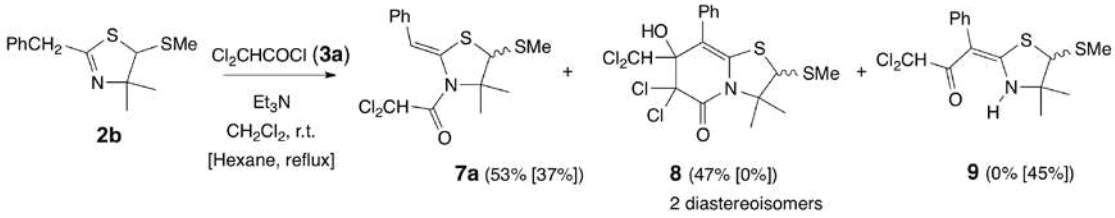
Scheme 1



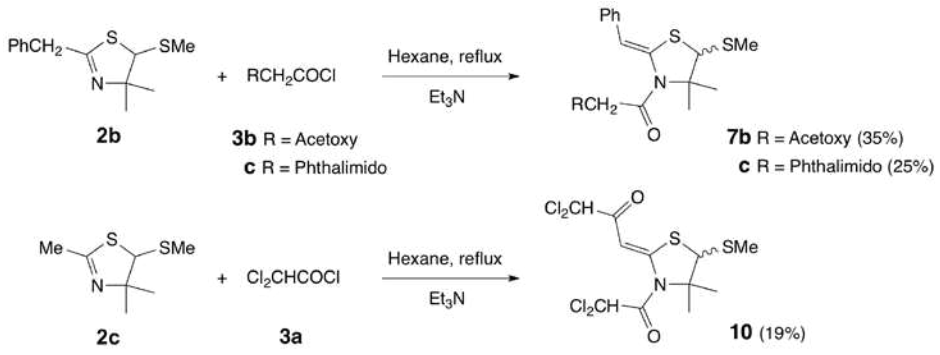
Scheme 2



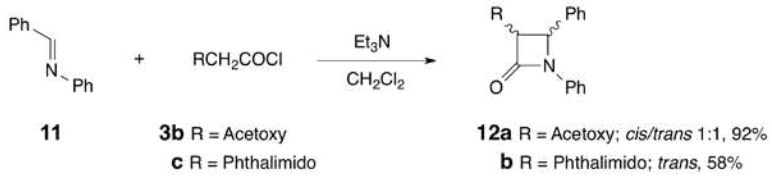
Scheme 3



Scheme 4

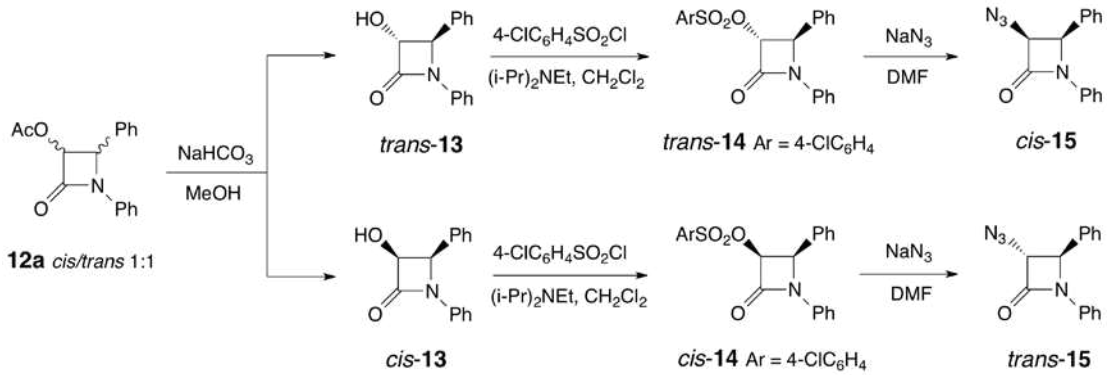


Scheme 5



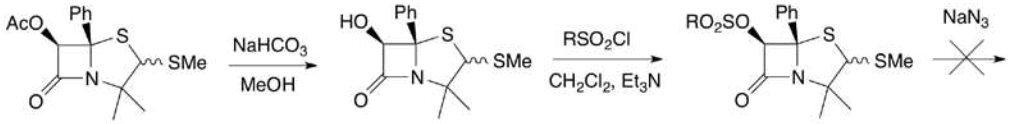
11 **3b** R = Acetoxy; **c** R = Phthalimido; **12a** R = Acetoxy; *cis/trans* 1:1, 92%; **b** R = Phthalimido; *trans*, 58%

Scheme 6



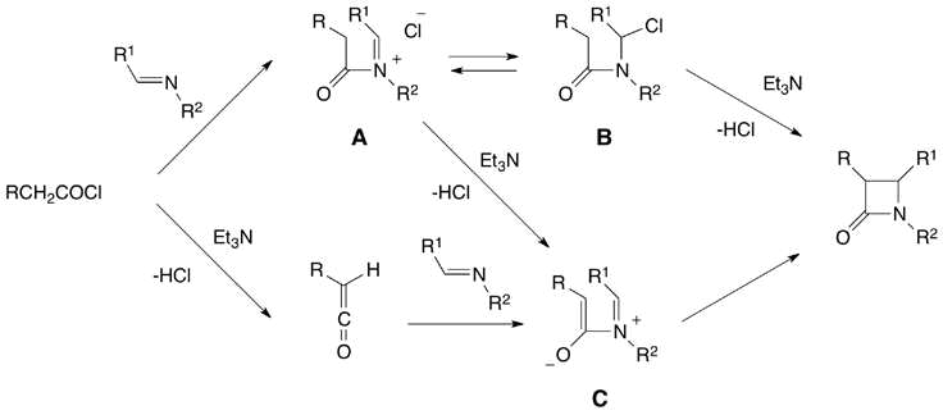
12a *cis/trans* 1:1

Scheme 7

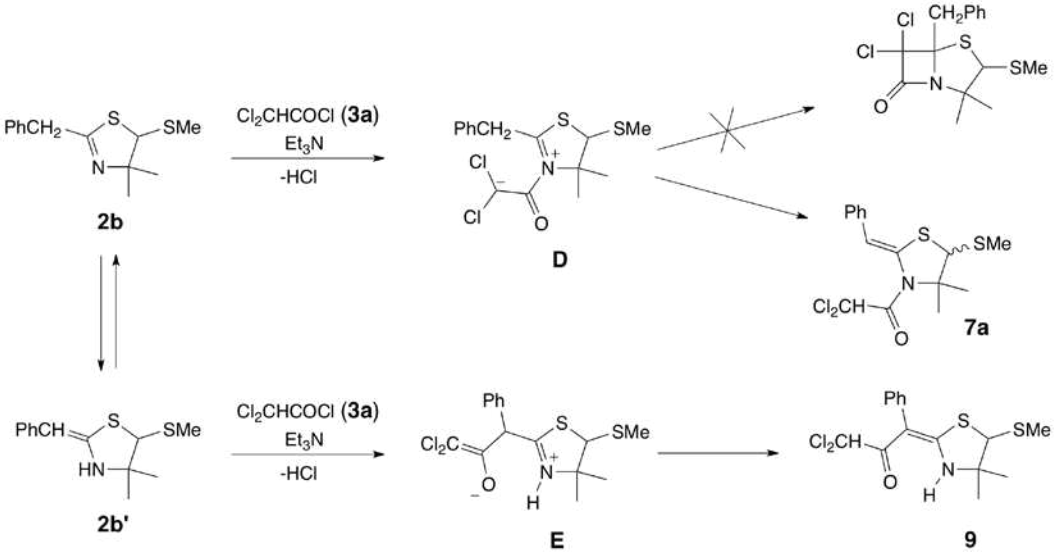


6a **16** **17a** R = 4-ClC$_6$H$_4$; **b** R = 2,4-(NO$_2$)$_2$C$_6$H$_3$; **c** R = F$_3$C

Scheme 8



Scheme 9



Scheme 10

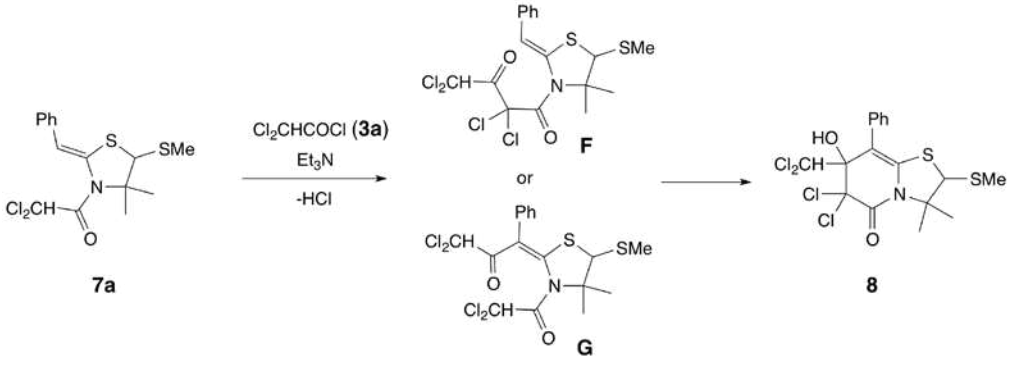


Figure 1

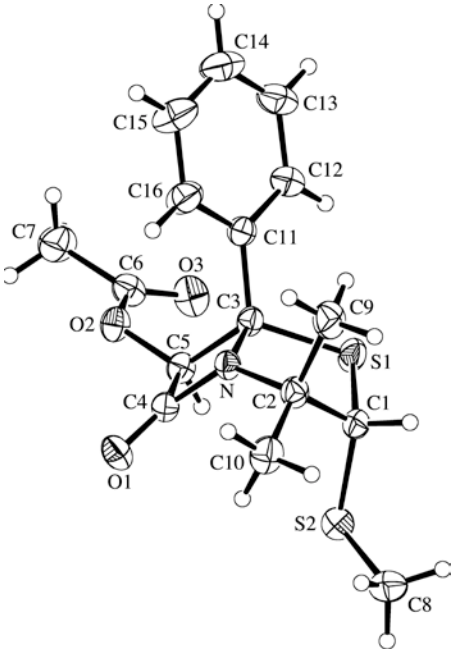
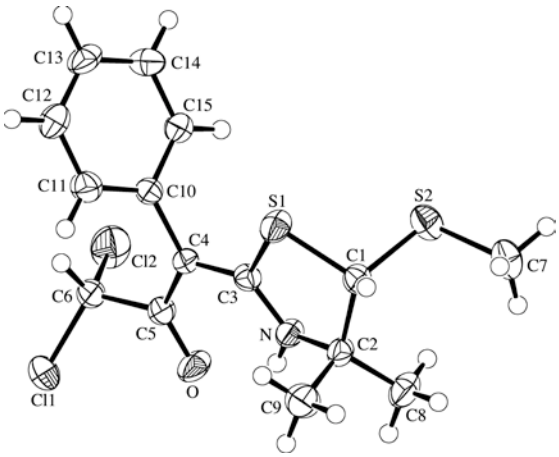

C14
C13
C15
C12
C16
C11
C7
C6
O3
C3
C9
O2
C5
S1
N
C4
C2
C1
C10
O1
S2
C8

Figure 2

a)



b)

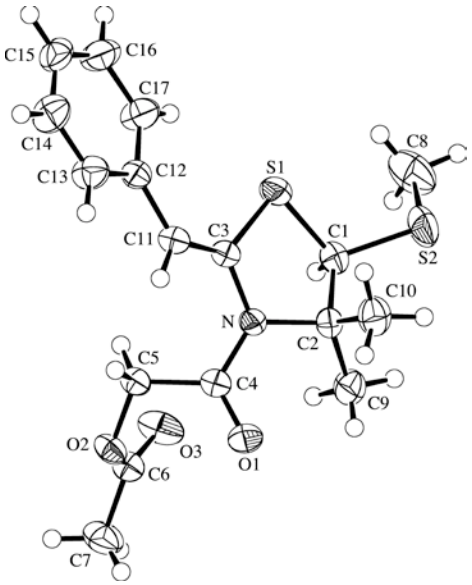
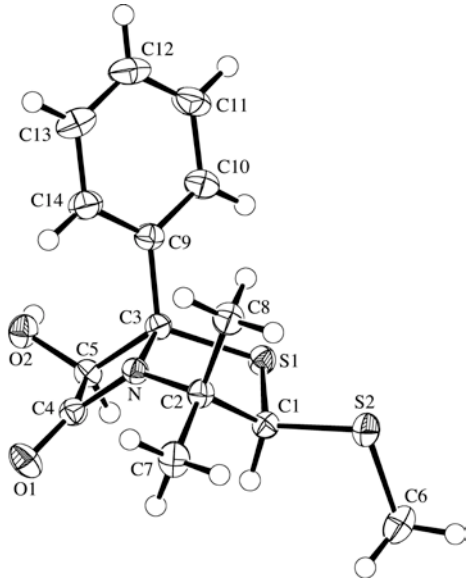


Figure 3



Graphical Abstract